

REMARKS/ARGUMENTS

With this amendment, claims 1-5 and 11-15 are pending. Claims 6-10 and 16-27 are withdrawn. For convenience, the Examiner's rejections are addressed in the order presented in a June 11, 2004, Office Action.

I. Status of the claims

Claims 1, 4, 5, 11, and 14-15 are amended to recite appropriate SEQ ID NOs, rather than reciting Figure numbers. These amendments add no new matter and are not limiting amendments. Claims 2 and 12 are amended to remove reference to UUBC9. These amendments add no new matter.

II. Claim objections

Claims 1-5 and 11-15 are objected to for referring to sequences in Figures 1 or 2 rather than referring to a sequence identifier. In order to expedite prosecution claims 1, 4, 5, 11, and 14-15 are amended to recite the appropriate SEQ ID NOs. In view of these amendments, Applicants respectfully request that the objections to the claims be withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 5, 11, and 15 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. According to the Office Action, the specification does not enable one of skill to make and/or use the invention commensurate in scope with the claims. In particular the Office Action alleges that "insufficient guidance is provided as to which protein will serve as a target for USP-25." Office Action at page 3. The Office Action also alleges that undue experimentation is required to practice the claimed invention. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to identify USP-25 target proteins for use in the claimed invention. However, the proper test of enablement is

“whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation” (*see, e.g.*, MPEP §2164.01). In the present application, one of skill would know how to avoid inoperative embodiments and to identify USP-25 target proteins, without undue experimentation (*see, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). Moreover, the present application provides guidance in the form of assays and working examples for identification of USP-25 target proteins.

Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. As described by the court in *In re Cook and Merigold*, 169 USPQ 302:

Many patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit ‘factors which must be presumed to be within the level of ordinary skill in the art’ There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such a manner as to make the embodiment operative rather than inoperative.

See, In re Cook and Merigold, 169 USPQ at 302 (quoting in part *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention (*see, Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)). As described in *Wands*, “a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed” (*see, Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982)).

The specification provides standard assays and working examples for determining USP-25 target proteins. USP-25 target proteins frequently bind to the USP-25 protein. The specification provides assays to detect binding of proteins to USP-25, including *e.g.*,

immunoprecipitation and western blotting at page 49, line 21 through page 50, line 6; and two hybrid assays at page 52, line 31 through page 52, line 30.

Characteristics of USP-25 target proteins that can be determined by those of skill based on the specification include *e.g.*, conjugation to ubiquitin or a ubiquitin-like protein, and modification of the USP-25 target protein-ubiquitin complex by USP-25. Assays to ubiquitinate a target protein or to detect modification of ubiquitination of a target protein are found *e.g.*, at page 48, line 13 through page 50, line 10.

Applicants respectfully assert that two hybrid screens for protein binding are routinely performed on thousands of candidate proteins. Identification of candidate proteins that bind to USP-25 can be efficiently accomplished with the disclosed two-hybrid assays. The additional disclosed binding, ubiquitin conjugation, and ubiquitin-specific protease assays can be performed quickly and efficiently on candidate target proteins by those of skill. Thus, undue experimentation is not required to identify those target proteins as asserted by the Office Action. Those of skill in the art would clearly be able to use the specification to efficiently identify appropriate target proteins and practice the methods of the invention for identifying bioactive agents that modulate USP-25 activity. Identification of operable embodiments, therefore, was well within the means of one of skill of the art, without undue experimentation.

Given the disclosure of the specification and the knowledge of those of skill in the art, the claimed invention is fully enabled. Applicants, thus, respectfully request withdrawal of the rejection for alleged lack of enablement.

IV. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1, 5, 11, and 15 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. According to the Office Action, the specification lacks description of the claimed invention, such that a skilled artisan would recognize that Applicants had possession of the claimed invention at the time of filing. The claims are directed to methods of identifying bioactive agents that modify a USP-25 protein, using a USP-25 target protein to assess the modification. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The basis of the rejection is that the specification allegedly provides adequate description of only three representative members of USP-25 target proteins, *e.g.*, SYK, calcineurin, and UBC9. Applicants assert that the application does provide support for the full concept of the claimed genus, and moreover, that the assays used to identify USP-25 target proteins used in the claimed methods were well known at the time of filing and the descriptions provided easily meet the properly applied standard of written description.

The Office Action appears to assert that the inventors were not in possession of the claimed invention at the time of filing because not all species of the claimed genus were reduced to practice. However, under United States patent law, invention refers to the inventor's conception of an idea, rather than to a physical manifestation of the idea, *e.g.*, actual reduction to practice. The United States Supreme Court has stated that "[i]t is well settled that an invention may be patented before it is reduced to practice." *Pfaff v. Wells*, 48 USPQ2d 1641, 1644 (U.S. Supreme Ct. 1998); *see also* MPEP 2163(II)(A)(2)(a). The applicant can demonstrate conception and satisfy the requirement for written description by describing the invention with "sufficient clearness and precision" to allow one of skill in the art to practice the invention as intended by the inventor. *Pfaff* at 1644. Reduction to practice is not required.

Moreover, according to the Federal Circuit, Applicants have some flexibility in the "mode selected for compliance" with the written description requirement. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886, 1896 (Fed. Cir. 2004). As indicated in the enclosed declaration, Applicants were the first to identify the USP-25 protein as a ubiquitin specific peptidase. Moreover, the claims are directed to assays for the modulation of a USP-25 protein and its target proteins. The claims are not directed to identification of new nucleic acids or proteins that can be used as target proteins. Rather, target proteins share a combination of characteristics that are fully described in the specification and that are recited in the claims. The MPEP is in agreement that not all biomolecules must be described using specific sequence information.

For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular

weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. . . [U]nique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. *See Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966 (“written description” requirement may be satisfied by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention”).

The concept of the claimed genus of methods, *i.e.*, identification of bioactive agents that modulate the activity of USP-25, is fully described in the specification, which includes recitation of a representative number of species for USP-25 target proteins used in the claimed methods, *i.e.*, SYK and calcineurin. The UBC9 protein was also identified as a USP-25 target protein and provides support for the genus of target proteins. The steps of the claimed methods are, *e.g.*, combining a USP-25 protein, a USP-25 target protein which is conjugated to ubiquitin or ubiquitin-like protein, and a candidate bioactive agent; and determining the level of ubiquitin-conjugated or ubiquitin-like protein-conjugated target protein in the presence and absence of said candidate bioactive agent. These steps do not appear to be at issue. Rather, the Office Action appears to focus on the description of the USP-25 target proteins used in the claimed methods.

USP-25 target proteins and their characteristics are adequately described in the specification and the description enables those of skill in the art to use the claimed methods. Moreover, the specification provides representative numbers of the genus of USP-25 target proteins, *i.e.*, SYK and calcineurin, and UBC9 proteins, as required by *Regents of the University of California v. Eli Lilly* 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) and MPEP 2163. Methods found in the specification were used to identify SYK, calcineurin, and UBC9 proteins as USP-25 target proteins and those methods can be used identify other members of the USP-25 target proteins genus that share the same characteristics. Characteristics of USP-25 target proteins that can be determined by those of skill based on the specification include *e.g.*, conjugation to

ubiquitin or a ubiquitin-like protein, and modification of the USP-25 target protein-ubiquitin complex by USP-25. Assays to ubiquitinate a target protein or to detect modification of ubiquitination of a target protein are found *e.g.*, at page 48, line 13 through page 50, line 10. Thus, one of skill would easily be able to distinguish a USP-25 target proteins from other proteins based on the assays described in the specification.

In view of the above amendments and remarks, withdrawal of the rejections under 35 U.S.C. §112, first paragraph, for alleged lack of written description is requested.

V. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-5 and 11-15 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Office Action alleges that the claims are indefinite for use of the phrase "protein activity." To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Applicants assert that one of ordinary skill in the art would understand the claimed invention in light of the specification. "[35 U.S.C.] §112, second paragraph, requires a determination of whether those skilled in the art would understand what is claimed in light of the specification." *Orthokinetics v. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986).

The claims clearly refer to USP-25 protein activity, which is clearly defined in the specification at page 45, lines 11-24. USP-25 protein activity includes, *e.g.*, "modulation of leukocyte activation; modulation of platelet activation; modulation of lymphocyte activation; modulation of B lymphocyte activation by BCR stimulation; modulation of T lymphocyte activation by TCR stimulation; modulation of mast cell activation by stimulation of surface IgE; modulation of B cell differentiation; modulation of lymphocyte proliferation; modulation of IgM, IgG induction in B lymphocytes; modulation of immunoglobulin heavy chain gene promoter activity in lymphocytes; modulation of NFAT gene promoter activity in lymphocytes; modulation of immunoglobulin secretion by B lymphocytes; modulation of cytokine production in leukocytes; modulation of surface protein expression including CD23, CD69, CD80 and CD 86 in lymphocytes; modulation of CD40L expression in primary T lymphocytes; modulation of

Nf-kB activity; modulation of IL-2 expression in primary T lymphocytes; binding to SYK, UBC9 and calcineurin; binding to ubiquitinated SYK, UBC9 and calcineurin; binding to SYK, UBC9, calcineurin and IκB protein conjugated to ubiquitin-like protein; ubiquitin-specific peptidase activity; ubiquitin-like protein specific peptidase activity; modulation of SYK, UBC9 and calcineurin activity; modulation of SYK, UBC9 and calcineurin protein levels."

Based on this definition, those of skill would understand what is meant by the phrase "protein activity" in the claims. In view of the above arguments, Applicants respectfully request withdrawal of the rejection.

VI. Rejections under 35 U.S.C. §103

Claims 1-5 and 11-15 were rejected as allegedly anticipated by WO 00/78934 to Nizetic *et al.* Applicants respectfully traverse the rejection, and herein provide evidence in the form of a declaration (Exhibit A) and evidence (Exhibit B) under 37 C.F.R. § 1.131 that the claimed subject matter was invented prior to the publication date of the cited reference. The declaration and evidence demonstrate that the inventors conceived and reduced to practice methods of identifying modulators of the ubiquitin peptidase activity of the USP-25 protein. In contrast, the later published Nizetic *et al.* reference disclosed a role for USP-25 only in identification of inhibitors of USP-25 that can be used for treatment of Alzheimer's disease. *See, e.g.,* Nizetic *et al.* at page 21, lines 8-11.

Applicants respectfully submit that the declaration and evidence provided in Exhibit B unequivocally establish that the claimed invention was conceived of and reduced to practice prior to December 28, 2000, the publication date of Nizetic *et al.* As the conception and reduction to practice predates publication of Nizetic *et al.*, the reference cannot properly be cited in a rejection for obviousness under 35 U.S.C. §103. Applicants therefore respectfully request that the rejection be withdrawn.

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Amdt. dated December 13, 2004
Reply to Office Action of June 11, 2004

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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